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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/892,613	06/27/2001	Shawn Shui-on Leung	655	4914

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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/892,613	LEUNG, SHAWN SHUI-ON	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 20-24* is/are pending in the application.

4a) Of the above claim(s) *14,15 and 20-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

1. The request filed on 12/9/03 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/892,613 is acceptable and a RCE has been established. Claims 1-13 are currently under prosecution. An action on the RCE follows.

2. Claims 14-15, 20-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions. Applicant timely traversed the restriction (election) requirement in Paper No. 14.

3. Claims 1-13 are under examination.

4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

5. The following Office Action contains NEW GROUNDS of rejection.

Rejections Withdrawn

6. The rejection of claims 1-13 under 35 U.S.C. 112, second paragraph, for parts (b), (c), (d), (g)-(i) in the last office action, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment to the claims.

7. The rejection of claims 16-19 under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification

does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description is withdrawn in view of the amendment to the claims.

Response to Arguments

8. The rejection of claims 1-13 under 35 U.S.C. 102(b) as being anticipated by Queen et al (U.S. Patent 5,693,762, issued 12/97, IDS #1 ½) is maintained.

The response filed 10/7/03 has been carefully considured but is deemed not to be persuasive. The response states that queen uses FR from one immunoglobulin. In response to this argument, because of the indefinite nature of the claims (see 112 second below) the claims are interpreted to be a re-engineered antibody that has FR from one source in a light or heavy chain and FR from a different source in the heavy or light chain respectively such that not all of the FR are from a single immunoglobulin chain. When the FRs are from one source in the light chain and the FRs are from a different source for the heavy chain this is interpreted to meet the limitation of "with the proviso that not all the replaced FR1, FR2, FR3, and FR4 are from the same framework of a single immunoglobulin chain". Thus the art of Queen et al reads on the claims.

The following are NEW GROUNDS of rejections

Claim Rejections - 35 USC § 112

9. Claims 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-13 are indefinite for reciting "heavy and/or light chain" in claim 1, line 2 and "heavy and light chain" in claim 1, line 6-7 because it is unclear if the claims uses both heavy and light chains or one or the other.

b. Claim 1 recites the limitation "said re-engineered immunoglobulin chain(s)" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

c. Claim 1 and those depended on claim 1 is indefinite for reciting "different immunoglobulin chains" because it is unclear if the frameworks are from the light chain and substituted for the heavy chain or visa versa or heavy chain are substituted for heavy and light for light chains or that the frameworks are from the light chain of one source and the frameworks from the heavy chain are from a different source.

d. Claims 6-9 are indefinite for reciting "which is the particular FR derived from a different source used for patching or that replaces the original FR of, the parent immunoglobulin" because it is unclear what the FR is from.

e. Claim 1-13 are indefinite for reciting "within ten-fold or within 3-fold" in claim 1 because does the claim mean 10 fold or three fold?

10. Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 1 has been amended to recite "within ten-fold". The response filed 12/9/03 did not state where support for the limitation can be found. The examiner found support for within 3-fold on page 12 but did not apparently find support for the within 10-fold limitation. Applicant is required to provide specific support for the limitation or remove it from the claim.

11. Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a re-engineered antibody comprising a heavy chain and a light chain wherein at least one of and FR1, 2, 3, 4, in the heavy chain or the light chain or both are replaced with the FR of the heavy or the light chain or both from the corresponding FR from a different species, wherein the antibody binds an antigen within three-fold of the parent antibody and wherein that not all of the replaced FR1, 2, 3, and 4 are from the same framework from a single immunoglobulin chain, does not reasonably provide enablement for a re-engineered antibody that has FR replaced in a heavy chain with those from another species in a light chain or visa versa wherein the antibody binds antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They

include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a re-engineered antibody that has FR of a heavy or light chain replaced with FR of a light or heavy chain respectively.

The specification teaches replacement of a FR of a heavy chain of one species with the same FR of a heavy chain from a different species. The claims are not commensurate in scope with the enablement provided in the specification.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions,

particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that proteins as defined by the claims which may contain FR from different regions such as FR1 or FR2 in a heavy or light chain in unspecified order have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Ohtomo et al (Molecular Immunology 32:407-416, 1995).

The claims are summarized as a re-engineered antibody comprising a heavy chain and a light chain wherein at least one of and FR1, 2, 3, 4, in the heavy chain or the light chain or both are replaced with the FR of the heavy or the light chain or both from the corresponding FR from a different species, wherein the antibody binds an antigen within three-fold of the parent antibody and wherein that not all of the replaced FR1, 2, 3, and 4 are from the same framework from a single immunoglobulin chain wherein the FR chosen has the highest homology to the parent FR, identical sequence of the parent FR, identical in three, four residues immediately adjacent to the flanking CDRs, wherein residues are reintroduced into the FR from residues from a different source wherein the reintroduced residues are those that are within 4 angstroms of a CDR wherein the re-engineered antibody has affinity of 108 M-1 and is pure and compositions with a pharmaceutical carrier.

Ohtomo et al teach a re-engineered antibody from a parent wherein FR4 is from the ND human antibody and the FR1-3 are from the EU human antibody (see abstract and Figure 2) wherein residues close to a CDR or indicated to influence antigen binding (from a molecular model, see page 408) are re-introduced into the FR (see abstract and page 412), wherein the re-engineered antibody binds antigen essentially with the same affinity as the parent (see Figure 3), wherein the antibody is pure and comprises BSA (see page 410).

Ohtomo et al is silent as to the affinity of the antibody or whether the residues are within 4 angstroms of a CDR, however, it is the examiners position that the antibody of Ohtomo et al has the same affinity and residues that are reintroduced are within 4 angstroms of a CDR as that claimed. One of ordinary skill in the art would reasonably conclude that Ohtomo et al antibody also possesses the same structural and functional properties as those of the antibodies claimed and, therefore, it appears that Ohtomo's antibodies are identical to the claimed antibody. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed antibody with the antibody of Ohtomo, the burden of proof is upon the Applicants to show a distinction between the structural and functional characteristics of the claimed antibody and the antibody of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

15. Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ohtomo et al (Molecular Immunology 32:407-416, 1995) and further in view of Queen et al (US Patent 5,693,762, issued 12/97, IDS #11/2).

The claims have been described supra. The claims also encompass replacing more than one FR with that from a different source and that more than one or two FR are not from the same FR of a single immunoglobulin chain and wherein the FR are at least 60% homology to the parent and close to a CDR and within 4 angstroms from a CDR and residues that interact with a CDR and residues that are typical are reintroduced.

Ohtomo et al has been described supra. Ohtomo et al does not teach replacement of more than two FR from a different source wherein more than two FR would not be from the same immunoglobulin chain or that the re-introduced residues are at least 60% homology to the parent or residues are adjacent to a CDR or replacing rare residues. This deficiency is made up for in the teachings of Queen et al.

Queen et al teach humanization of antibodies wherein the FR are compared to human FR and the FR chosen are at least 70% homology to the parent and residues

that are re-introduced are within 3 angstroms of a CDR or influence binding or interact with a CDR or is rare at that position and the affinity should be within two fold of the parent (see column 2-3).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced the claimed invention of replacing FR with human FR from any human antibody that has the most homology and re-introducing residues that influence binding in view of Ohtomo et al and Queen et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced the claimed invention of replacing FR with human FR from any human antibody that has the most homology and re-introducing residues that influence binding in view of Ohtomo et al and Queen et al because Ohtomo et al teach antibodies with FR from two human antibodies wherein the FR were chosen for highest homology with the parent FR.

In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced the claimed invention of replacing FR with human FR from any human antibody that has the most homology and re-introducing residues that influence binding in view of Ohtomo et al and Queen et al because Queen et al teach humanization by replacing FR with those that are the most homologous human FR and then re-introducing residues that influence antigen binding, are within 3 angstroms of a CDR or are rare at that position in the human FR.

In addition it would have been obvious to one of ordinary skill in the art to produce an antibody that had FR from different human antibodies because both

Ohtomo et al and Queen teach that FR influence the CDRs and antigen binding and one wants the highest homology between the parent FR and the human FR that is to be substituted so one does not need to re-introduce many residues as taught by Ohtomo et al "the number of changes in the human FRs, however, should be minimized" (see page 414). In addition, it would have been obvious to produce the claimed invention because Ohtomo et al teach there approach is that human FRs are chosen based on the identification of the most homologous sequence (see page 414). Thus it would have been obvious look at the FR and pick the most homologous regardless of whether they are from two or more antibody sequences.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 6:30 am to 4:00 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (571) 272-0871.

18. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

571-272-0832

LARRY R. HELMS, PH.D
PRIMARY EXAMINER